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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,660	PROVINS ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,20 and 26-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6,9,11-13,20,32 and 33* is/are rejected.

7)☒ Claim(s) *1-3,7,8,10,14-17 and 26-31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

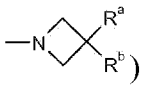
Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17, 20 and 26-33 are pending in this application.

Election/Restrictions

Applicant's election of Group I (claims 1-17, 20 and 26-33 drawn to compounds of formula (I) wherein Y is –NH-R^2 wherein R^2 is cycloalkyl; or Y is ) in the reply filed on May 1, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-7, 15-20, 26, 28, 30 and 32 (**all in part, drawn to compounds of formula (I) wherein Y is –NH-R^2 and R^2R^3 together is an alkylene bridge**) are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 1, 2008.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 32 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating COPD, does not reasonably provide enablement for a method of treating respiratory disorders in connection with Chronic Obstructive

Pulmonary Disease or for treating symptoms related to chronic bronchitis, emphysema, cough, cystic fibrosis, pulmonary fibrosis, adult respiratory distress syndrome, rhinitis or asthma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The scope of the claims is not adequately enabled solely based on the activity related to PDE IV activity provided in the specification. Claims recite 'a method of treating respiratory disorders in connection with Chronic Obstructive Pulmonary Disease or for treating symptoms related to chronic bronchitis, emphysema, cough, cystic fibrosis, pulmonary fibrosis, adult respiratory distress syndrome, rhinitis or asthma'. The instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as pharmaceutical therapeutic agents as muscarinic receptor and PDE IV activity, useful to treat a wide list of diseases, which include respiratory disorders, chronic bronchitis, ARDS, etc. Pharmacological data provided at pages 58-60 is drawn to a test the affinity of the compounds for human muscarinic receptors and PDE

IV enzymatic activity, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced by the instant claims.

The state of the art provides the unpredictability of the pharmacological therapeutic interventions related to COPD. See for example, Fox et al. (Drug Discovery Today: Disease Models 2004) provide: "Despite recent progress there is still a long way to go before we have a thorough comprehension of this debilitating disease. COPD patients currently have a poor prognosis, relatively ineffective therapy and reduced quality of life. Continued research using *in vitro* and *in vivo* models of COPD is crucial for progressing our understanding of this disease and to develop effective therapeutics" (see page 326). Cazzola et al. (TRENDS in Pharmacological Sciences 2007) indicate that: "The emerging recognition that COPD is a complex disorder, characterized by systemic inflammation in addition to local pulmonary inflammation, which might adversely impact on various extrapulmonary organs, such as the blood vessels and the heart, among others, emphasizes the need for more research on the underlying cellular and molecular mechanisms to discover new and more effective forms of therapy for this debilitating disorder. However, such an approach does not seem to be sufficient. In fact, unfortunately, a large number of crucially important questions remain unanswered [63]. For example, we still do not know whether treatment of lung inflammation decreases the risk of acute cardiac events, progression of atherosclerosis and/or thrombotic events. It is also unclear whether, alternatively, the treatment of heart disease can affect the progression of lung disease" (see page 549). Barnes et al. (Current Opinion in Pharmacology 2008) provide: "it will be difficult to demonstrate the efficacy of novel treatments on the rate of decline in lung function, since this requires large studies over three years. Hence, there is a need to develop novel outcome measures and surrogate

biomarkers, such as analysis of sputum parameters (cells, mediators and enzymes) or exhaled condensates (lipid mediators and reactive oxygen species) [6]. The use of imaging techniques, such as high resolution computerized tomography (CT) to measure disease progression is another promising approach as scanning resolution increases [50]. It may also be important to more accurately define the presence of emphysema versus small airway obstruction using CT scans, as some drugs may be more useful for preventing emphysema, whereas others may be more effective against the small airway inflammatory-fibrotic process. More research on the basic cellular and molecular mechanisms of COPD and on more useful animal models is urgently needed to aid the logical development of new therapies for this common and important disease, for which no effective preventative drugs currently exist" (see page 305).

As can be seen from above, the state of the art clearly establishes the unpredictability in therapeutic interventions using prostaglandin D2 antagonists. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-6, 9 and 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the claims, the recitation "…. cycloalkyl, **preferably** cyclopropyl, …." (**all occurrences**) is confusing and indefinite. Use of the term "preferably" through out the claims is indefinite and must be removed. See claim 4, line 2; claim 5, line 3; claim 6, line 2; claim 9, line 4; claim 11, line 2; claim 12, line 2; and claim 13, lines 3 and 4. In the above recitation, the term "preferably" is not acceptable because a subgenus is claimed within a genus. The term renders

the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention.

Allowable Subject Matter

Claims 1-3, 7-8, 10, 14-17, and 26-31 are objected to, for having non-elected subject matter. Claims 4-6, 9 and 11-13 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. The references of record do not teach or fairly suggest the instantly claimed compounds, see for example, US 3,624,084.

The claims would be allowable if the claims are amended to delete the recitations:

"or R^2R^3 is an alkylene bridging group" (claim 1, line 10);

"when Y is -NHR^2 and R^2R^3 is an alkylene bridging group or" (claim 1, line 20);

"or R^2R^3 is a C2-4-alkylene bridging group" (claim 3, line 5);

"or R^2R^3 is an alkylene bridging group selected from ethylene, propylene and butylene" (claim 5, line 5).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

August 7, 2008